AMERICAN ACADEMY OF OPHTHALMOLOGY®

Consensus Guidelines for Ocular Surveillance of von Hippel-Lindau Disease

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Purpose: To develop guidelines for ocular surveillance and early intervention for individuals with von Hippel-Lindau (VHL) disease.

Design: Systematic review of the literature.

Participants: Expert panel of retina specialists and ocular oncologists.

Methods: A consortium of experts on clinical management of all-organ aspects of VHL disease was convened. Working groups with expertise in organ-specific features of VHL disease were tasked with development of evidence-based guidelines for each organ system. The ophthalmology subcommittee formulated questions for consideration and performed a systematic literature review. Evidence was graded for topic quality and relevance and the strength of each recommendation, and guideline recommendations were developed.

Results: The quality of evidence was limited, and no controlled clinical trial data were available. Consensus guidelines included: (1) individuals with known or suspected VHL disease should undergo periodic ocular screening (evidence type, III; evidence strength, C; degree of consensus, 2A); (2) patients at risk of VHL disease, including first-degree relatives of patients with known VHL disease, or any patient with single or multifocal retinal hemangioblastomas (RHs), should undergo genetic testing for pathologic VHL disease gene variants as part of an appropriate medical evaluation (III/C/2A); (3) ocular screening should begin within 12 months after birth and continue throughout life (III/C/2A); (4) ocular screening should occur approximately every 6 to 12 months until 30 years of age and then at least yearly thereafter (III/C-D/2A); (5) ocular screening should be performed before a planned pregnancy and every 6 to 12 months during pregnancy (IV/D/2A); (6) ultra-widefield color fundus photography may be helpful in certain circumstances to monitor RHs, and ultra-widefield fluorescein angiography may be helpful in certain circumstances to detect small RHs (IV/D/2A); (7) patients should be managed, whenever possible, by those with subspecialty training, with experience with VHL disease or RHs, or with both and ideally within the context of a multidisciplinary center capable of providing multiorgan surveillance and access to genetic testing (IV/D/2A); (8) extramacular or extrapapillary RHs should be treated promptly (III/C/2A).

Conclusions: Based on available evidence from observational studies, broad agreement was reached for a strategy of lifelong surveillance and early treatment for ocular VHL disease. These guidelines were endorsed by the VHL Alliance and the International Society of Ocular Oncology and were approved by the American Academy of Ophthalmology Board of Trustees.

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Von Hippel-Lindau (VHL) disease is a rare autosomal dominantly inherited multisystem neoplastic condition caused by mutation in the *VHL* gene.[1] Cardinal manifestations include retinal hemangioblastoma (RH), central nervous system hemangioblastoma, renal cell carcinoma, pheochromocytoma, endolymphatic sac tumor, broad ligament and epididymal cystadenomas, pancreatic neuroendocrine tumors, and renal and pancreatic cysts.[2,3] In 1993, Latif et al[4] identified the VHL tumor suppressor gene, located on chromosome 3 (3p25−26). The product of the gene, the VHL protein, plays a critical role in cellular oxygen sensing. In the absence of normal VHL protein, hypoxia-inducible factors inappropriately induce expression of a wide array of target genes that normally coordinate a cell's response to hypoxia.[5-7]

Retinal hemangioblastoma is a benign, highly vascular neoplasm of the neurosensory retina that can occur in sporadic solitary form or as a common manifestation of VHL disease. Typically asymptomatic at early stages, RHs can cause vision loss secondary to tumor-associated exudation, fibrosis, hemorrhage, or retinal detachment as they grow.[8] Extrapapillary RHs, defined as those that arise more than 1.5 mm from the optic disc, initially appear as a red or grayish pinpoint lesion with diameter of less than 500 μm, similar in appearance to a microaneurysm or small intraretinal hemorrhage. Larger tumors are

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